

Enzyme Regulation

MUDR. MARTIN VEJRAŽKA, PHD.



Enzyme regulation

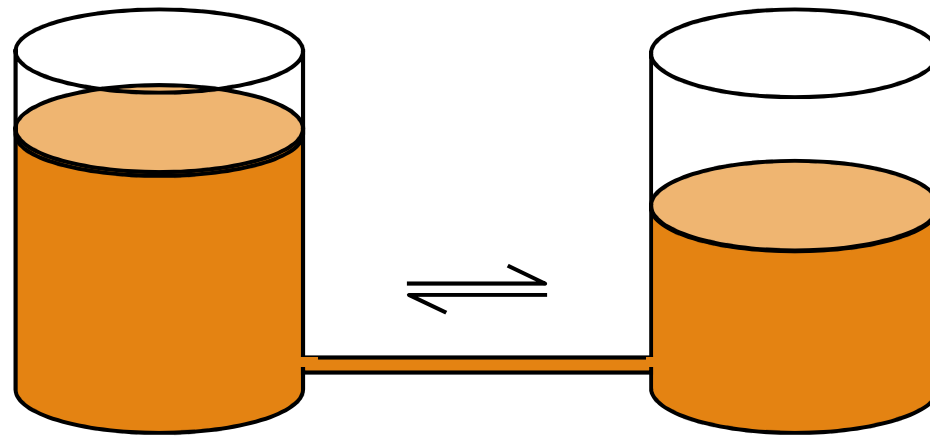
Body IS NOT in chemical equilibrium

Equilibrium = death

Life: Homeostasis, steady-state...



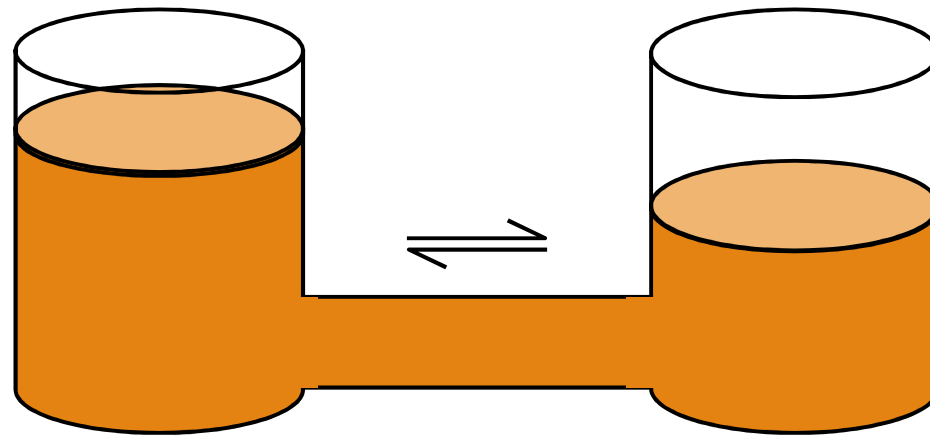
Catalysis in a closed system



Without catalyst
Equilibrium is set up slowly



Catalysis in a closed system

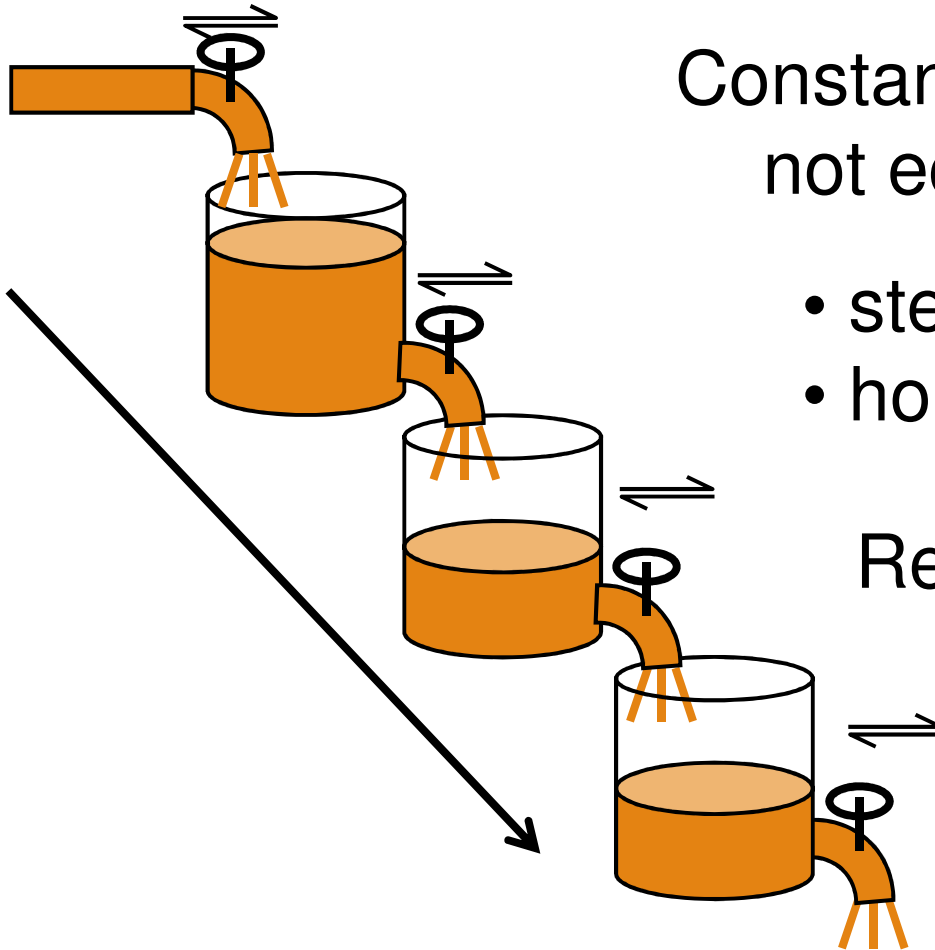


With a catalyst

The same equilibrium as w/o catalyst
but much faster



Opened system



Constant values but
not equilibrium

- steady-state
- homeostasis

Regulation changes values
(not only time to reach them)

Enzyme regulation

Controls concentrations

Corresponds to

- needs
- delivery



Enzyme regulation

Disrupted regulation causes disease

- Kinases and phosphatases: cancer
- Excess of some substance
(cholesterol – atherosclerosis,
uric acid – gout...)



Laboratory diagnostics

↑ or ↓ of concentration of some substance
↑/↓ formation / elimination

or

Measuring activity of an enzyme



Drugs

Many drugs change
activity of some
enzyme

(mostly inhibitors)

acetylosalicylic acid

simvastatine

allopurinol

omeprazole

sildenafil

vincristine

tetracycline

subactam

atorvastatine

enalaprile

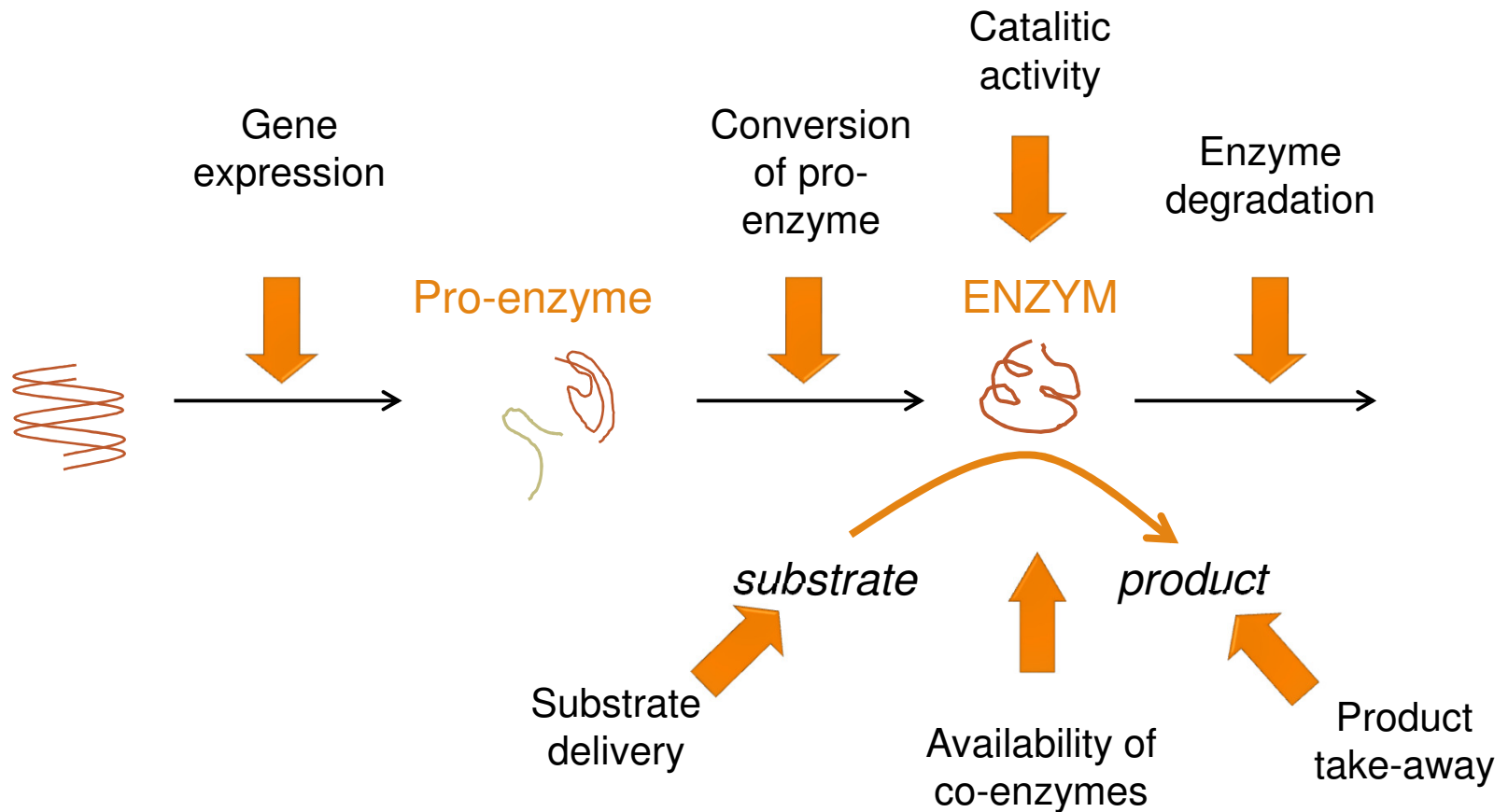
co-trimoxazole

Enzymes and drugs

Effect of many drugs is changed by action of enzymes

- cytochrome P₄₅₀
- conjugation
- acetylation
- ...

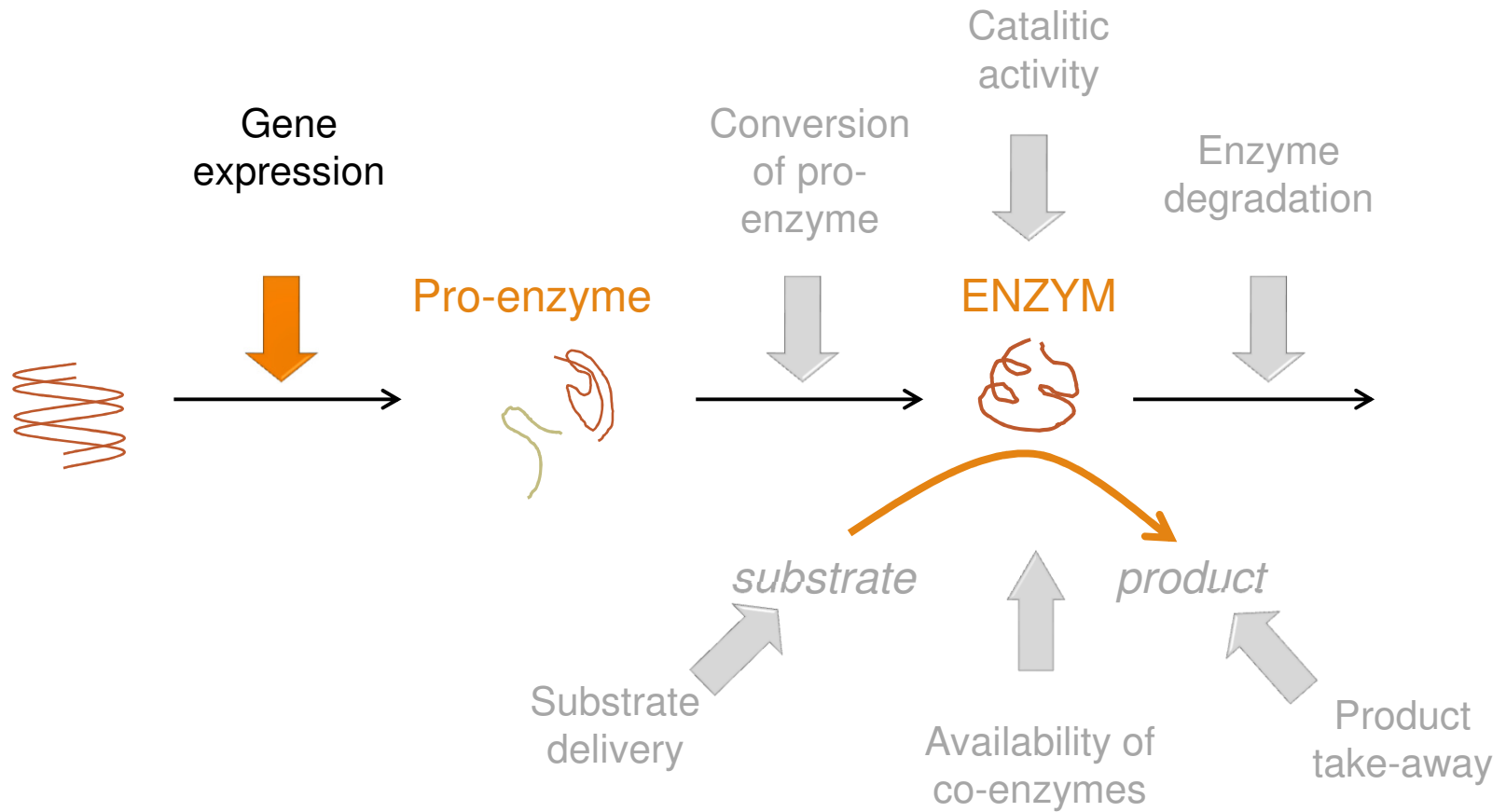
Enzyme regulation



Concentration of enzyme

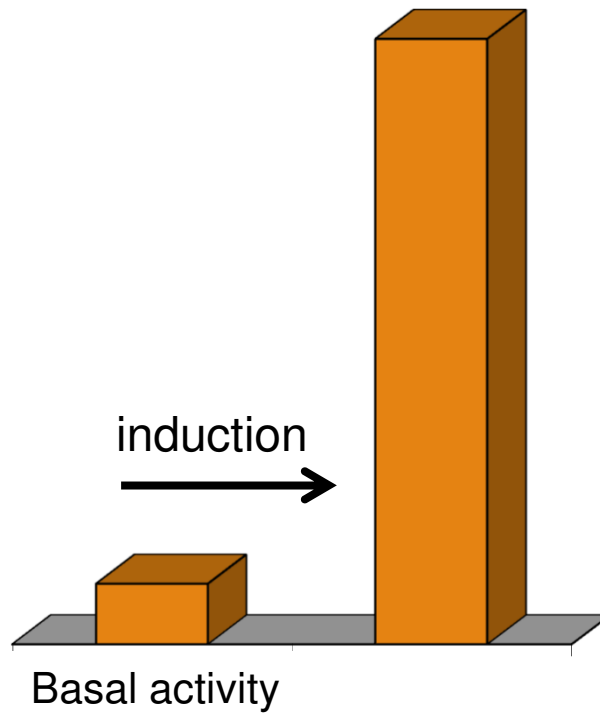


Induction and repression

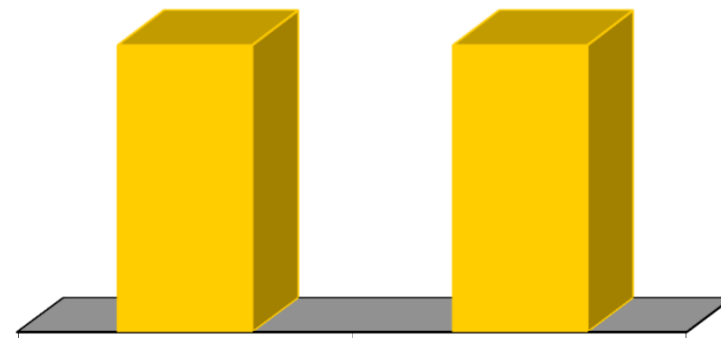


Induction

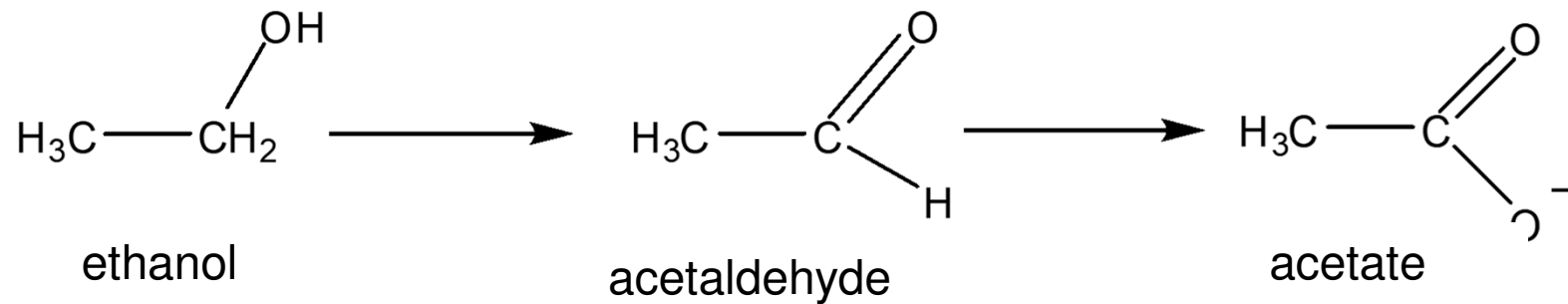
Inducible enzyme



Constitutive enzyme



Induction

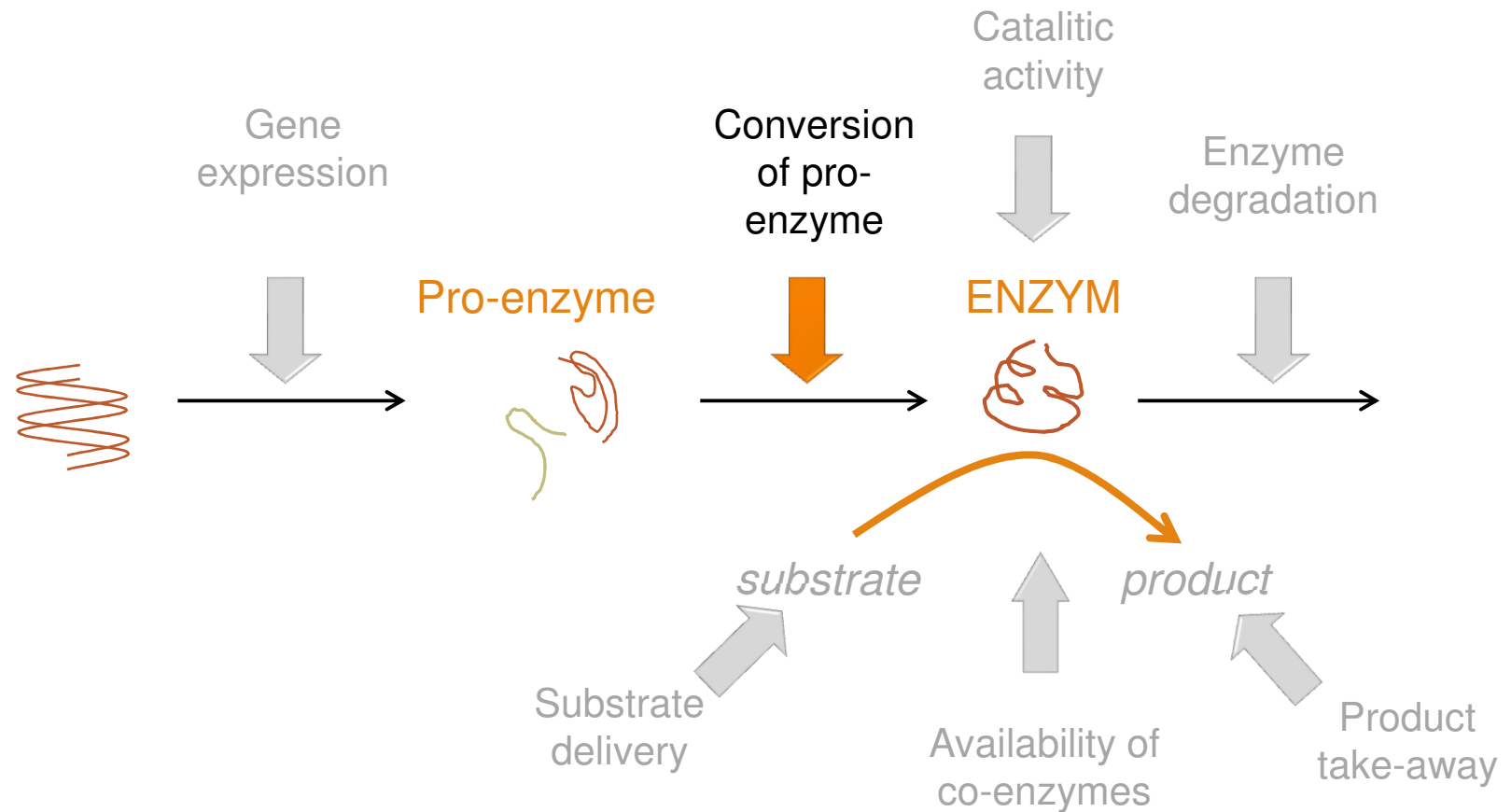


1. Alcohol dehydrogenase and aldehyde dehydrogenase
- constitutive enzymes
2. MEOS
- inducible

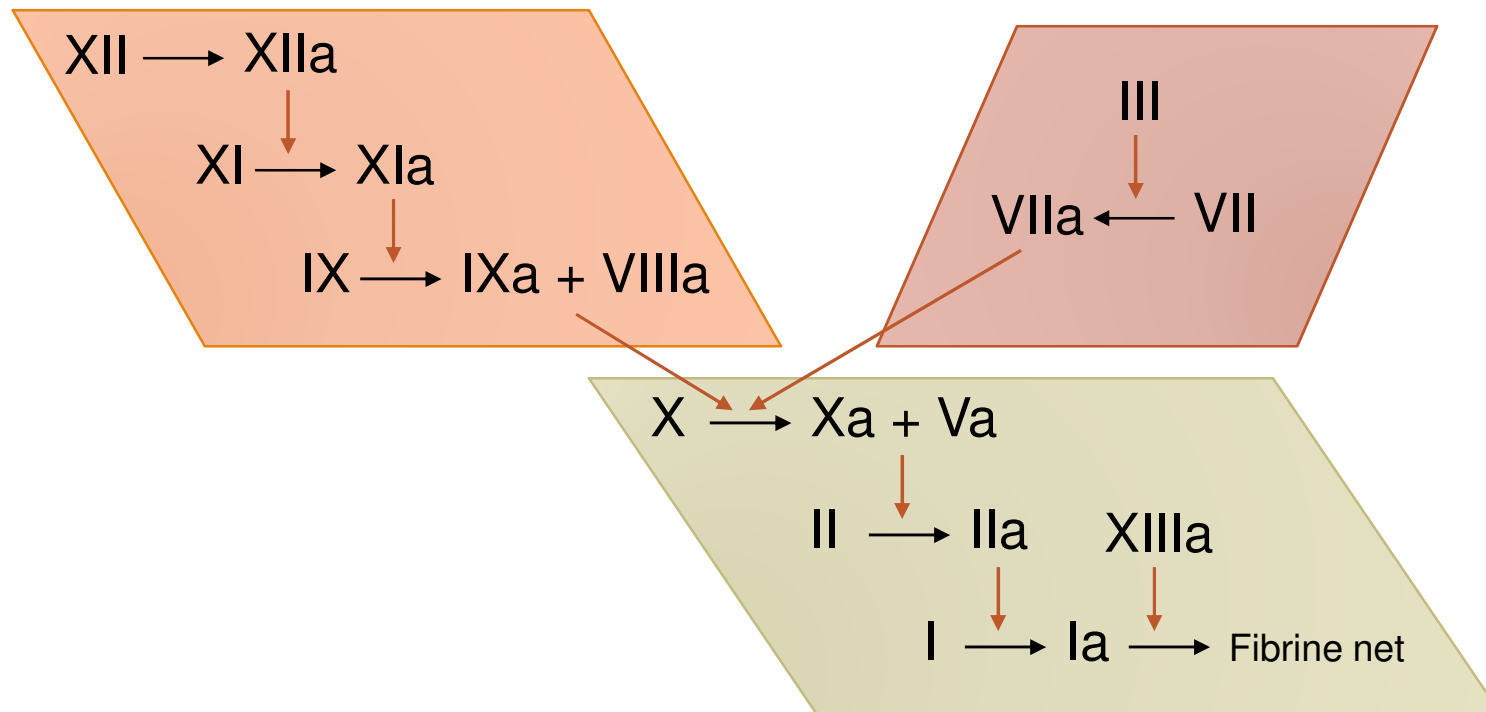
Repression



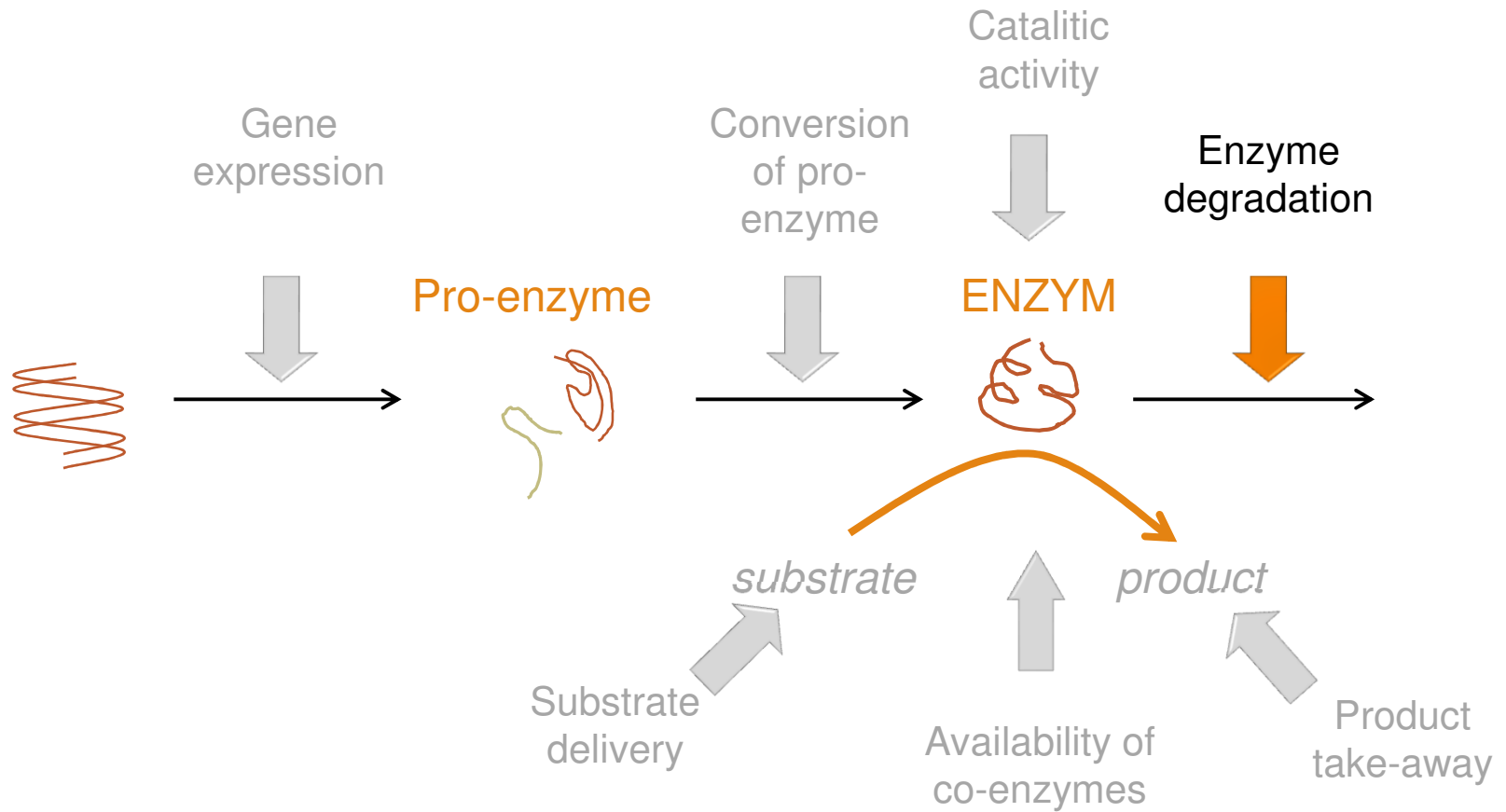
Conversion of pro-enzyme



Blood clotting



Degradation of enzyme



Degradation of enzyme

Often depends on conformation

Enzyme with substrate bound to active site is protected



Degradation of enzyme

Grapefruit juice increases degradation of intestinal cytochrome P450

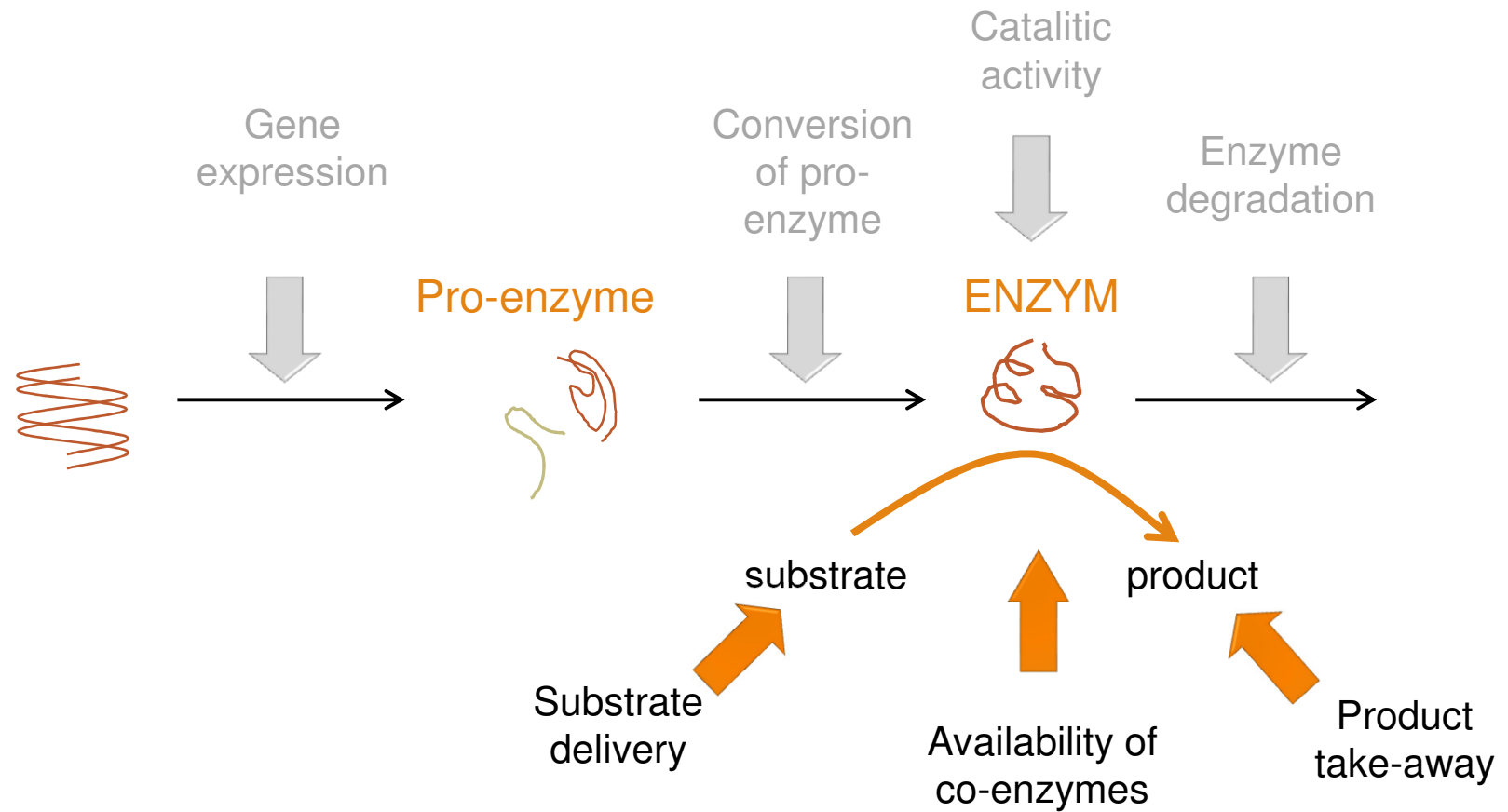
- Activity drops by one half within several hours
- Availability and effect of many drugs is increased



Substrate delivery



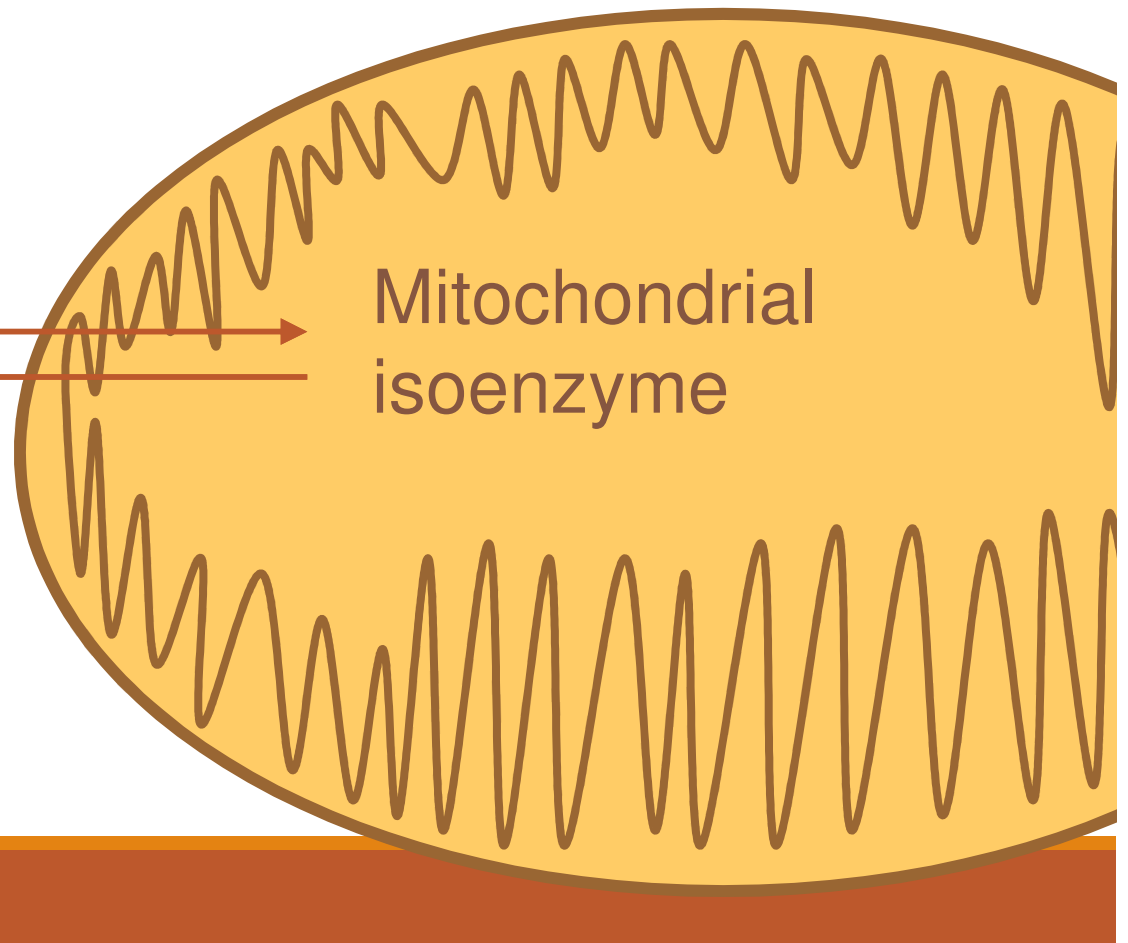
Concentration of substances



Compartments

Cytosolic
isoenzyme

Mitochondrial
isoenzyme



Compartments

Macromolecular complexes of enzymes

- Passing substrates - products, high local concentrations
- Transfer of conformational changes

Substrate concentration

Substrate concentration

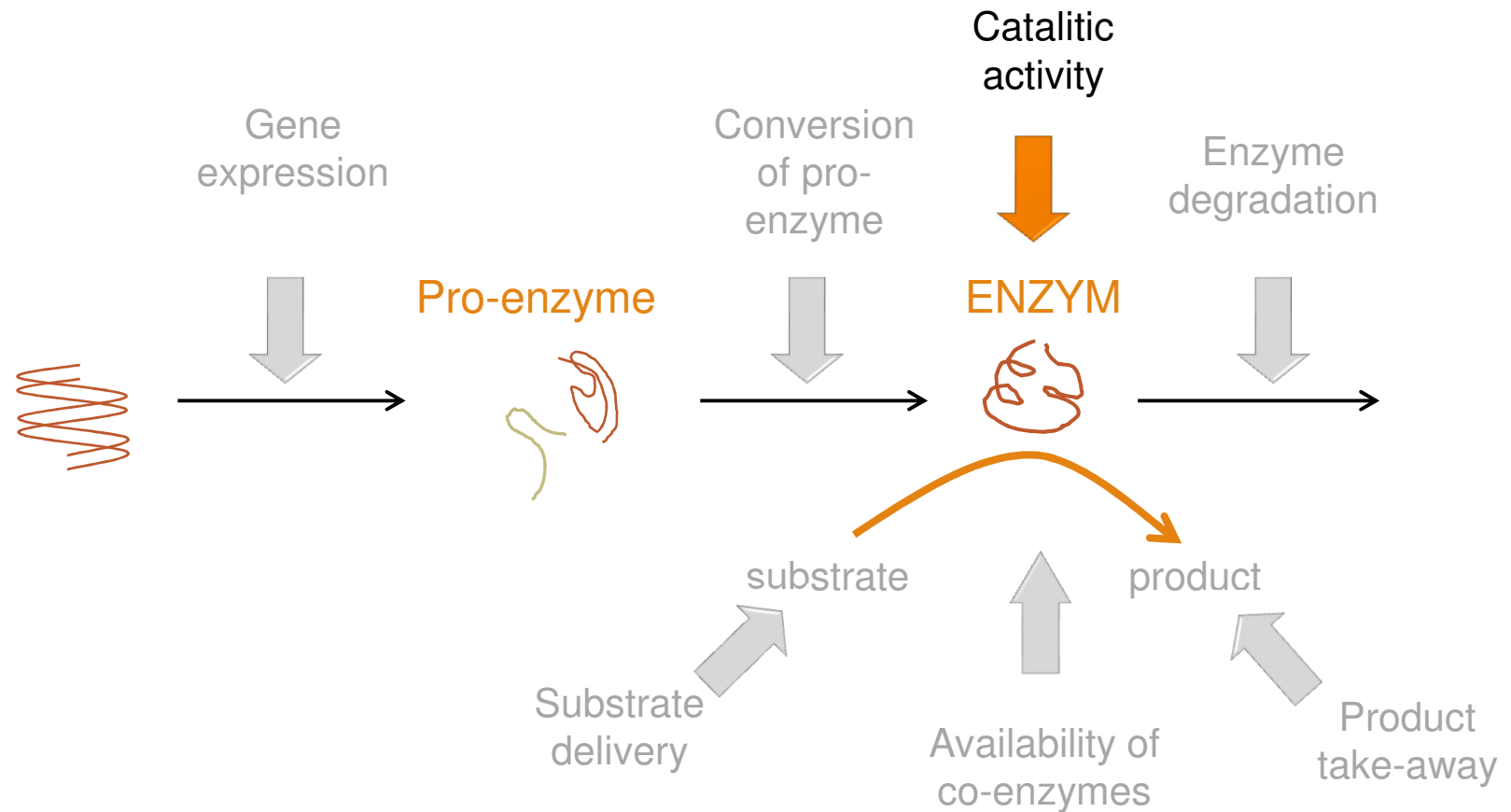
≠

Concentration of free substrate

Catalytic efficacy



Catalytic efficacy



Catalytic efficacy

Inhibitors

- drugs, poisons

Allosteric modification

Small molecules

Covalent modifications

Interactions between subunits



Inhibitors

Competitive

- Compete with substrate

Other

- Non-competitive, acompetitive, mixed

Competitive inhibition

Inhibitor often resembles substrate

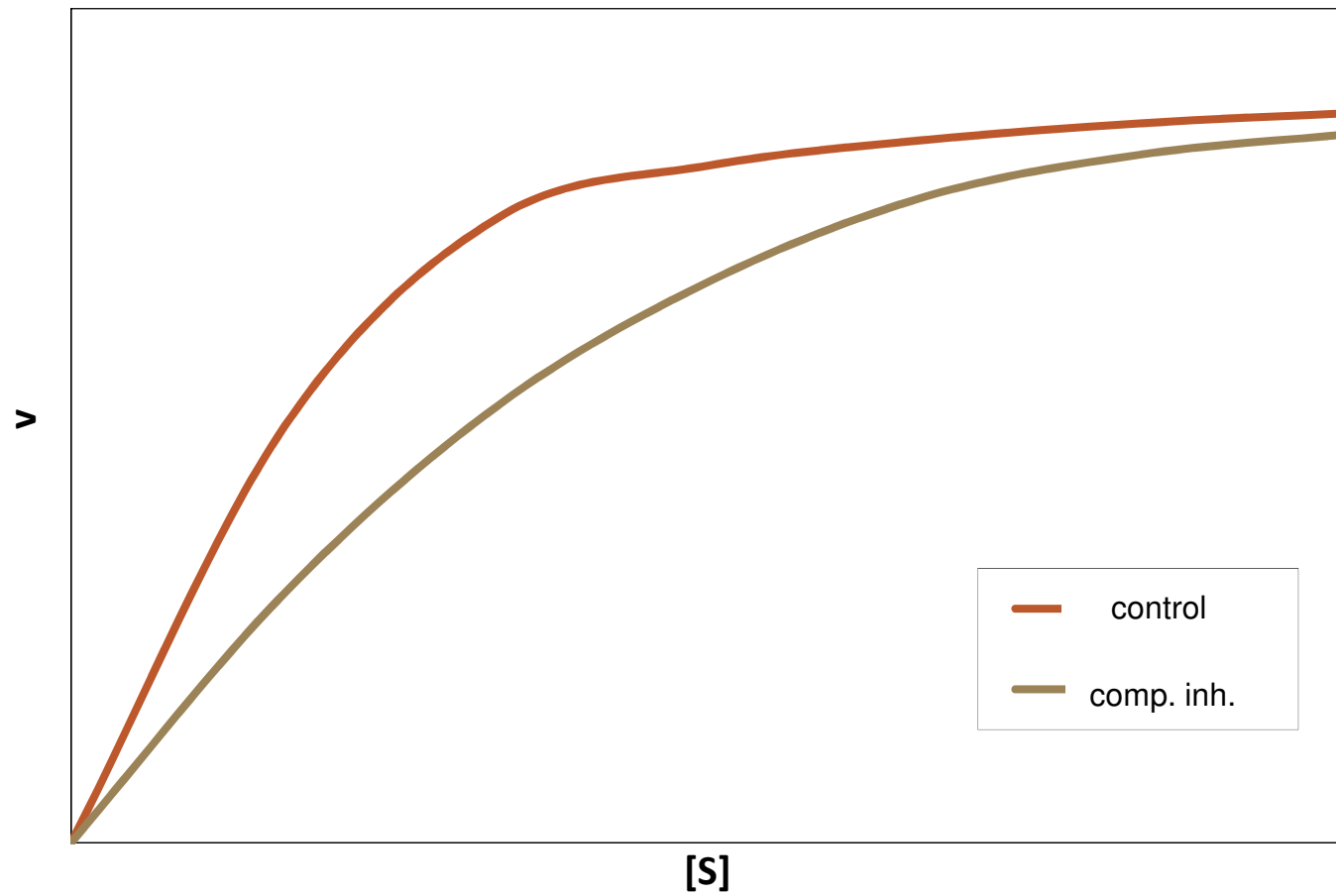
Effect depends on

- Concentration ratio
- Affinity ratio

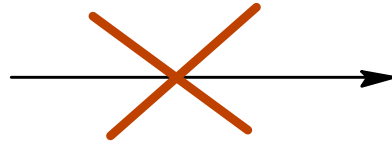
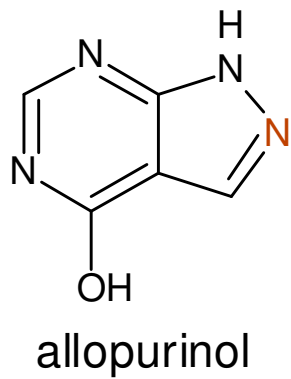
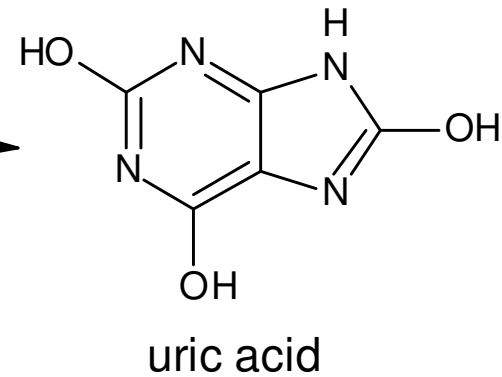
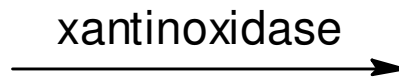
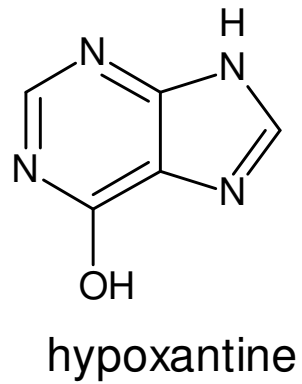
Reversible



Competitive inhibitors



Competitive inhibition



Noncompetitive inhibition

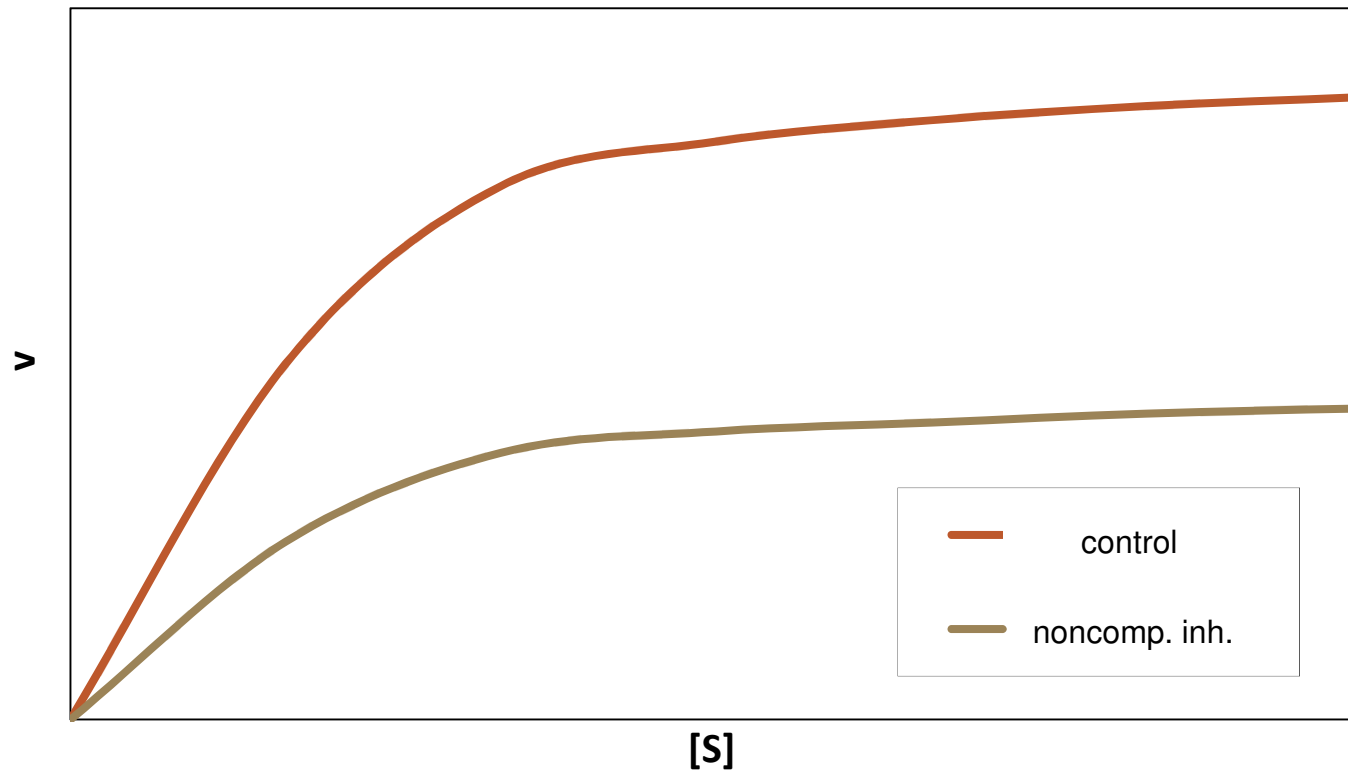
Inhibitor does not compete with substrate

Decreases amount of working enzyme

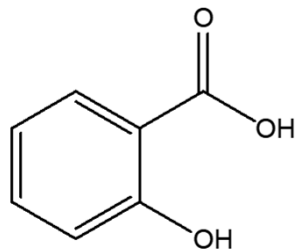
Reversible or irreversible



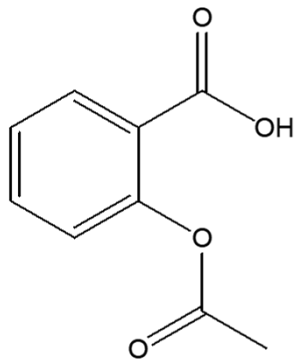
Noncompetitive inhibitors



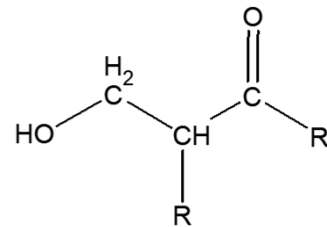
Noncompetitive inhibitor



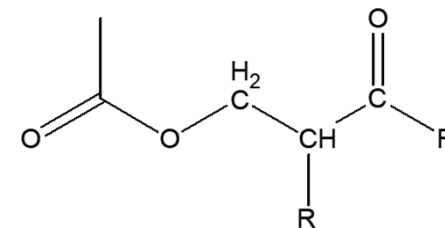
Salicylic acid



Acetylsalicylic acid



Ser



Photos from Bayer Health Care:

<http://www.aspirin.cz/aspirin/world/history/1/index.asp> (11/2007)

Allosteric regulation



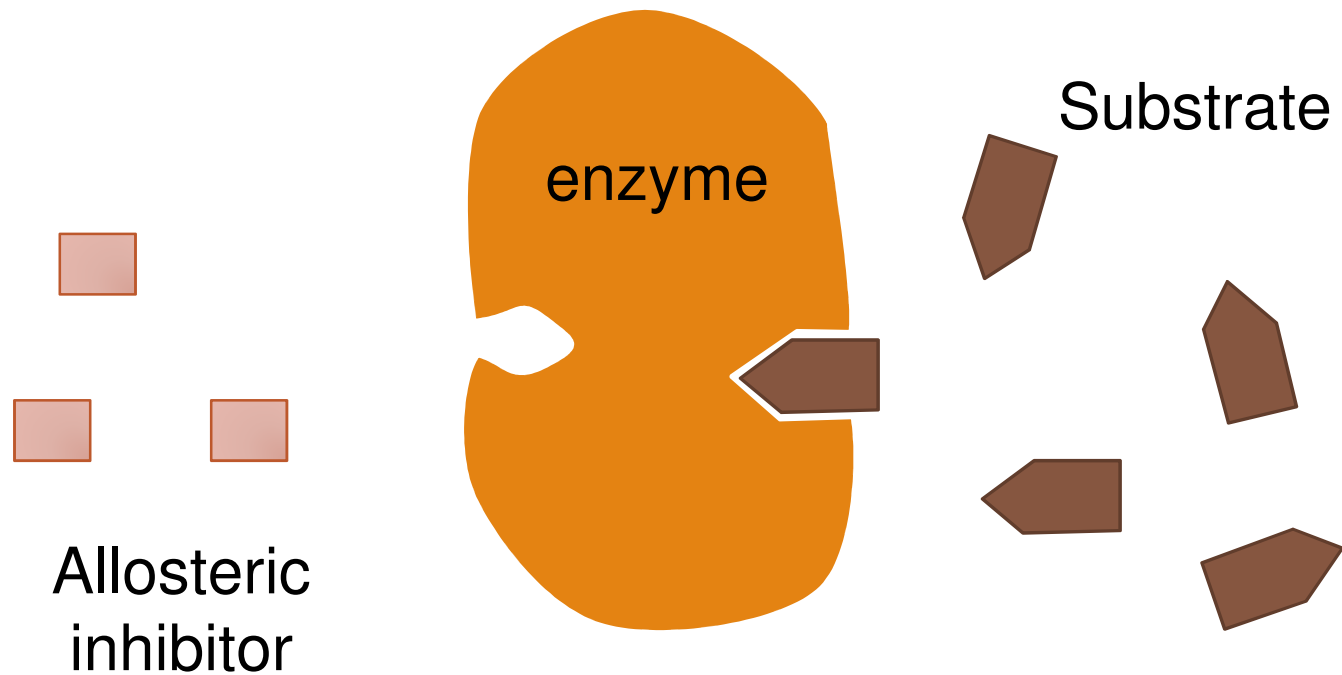
Allosteric modifiers

Do not resemble substrates nor co-enzymes

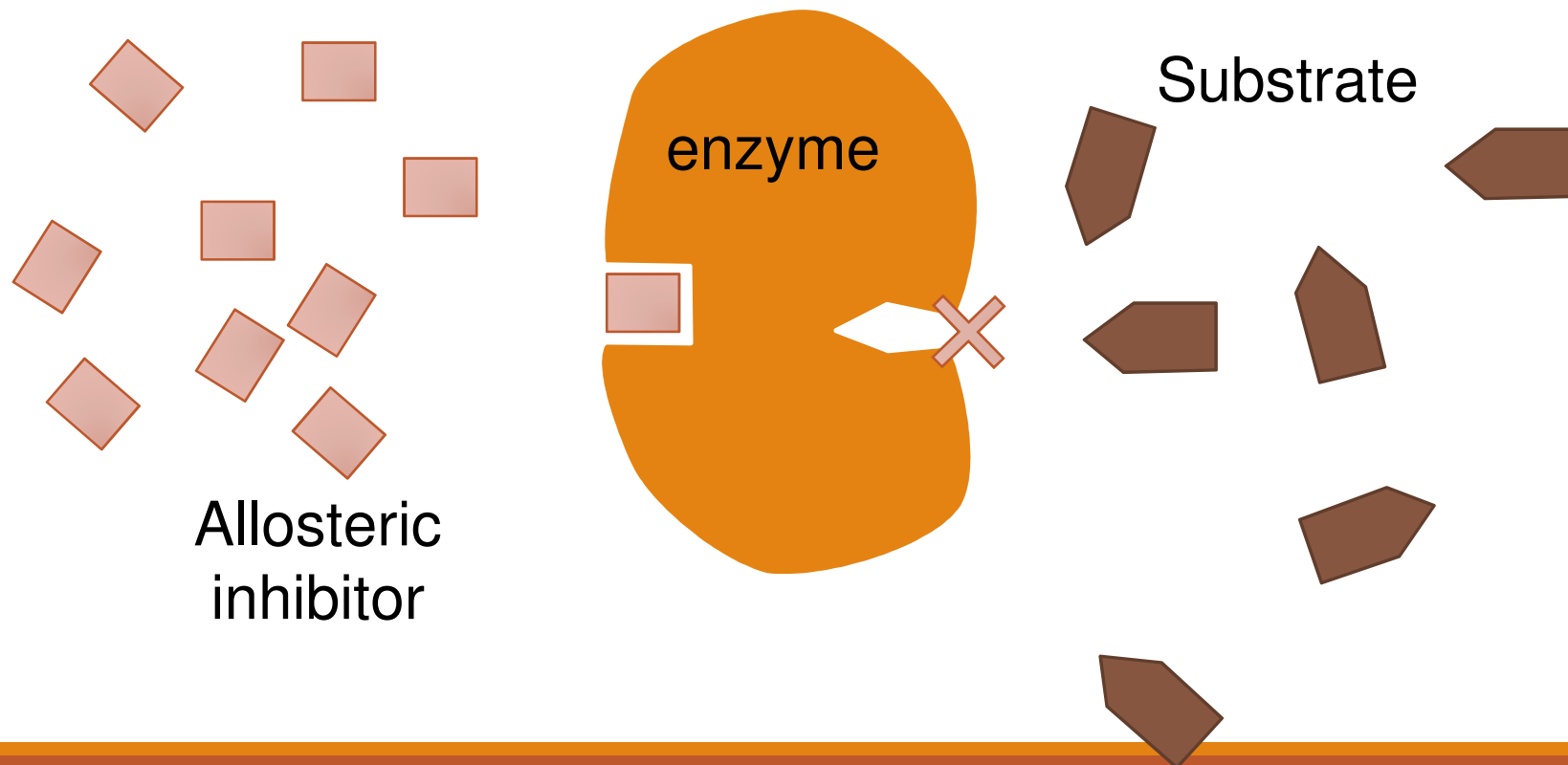
Bind to a site distant from active site

Change conformation of enzyme

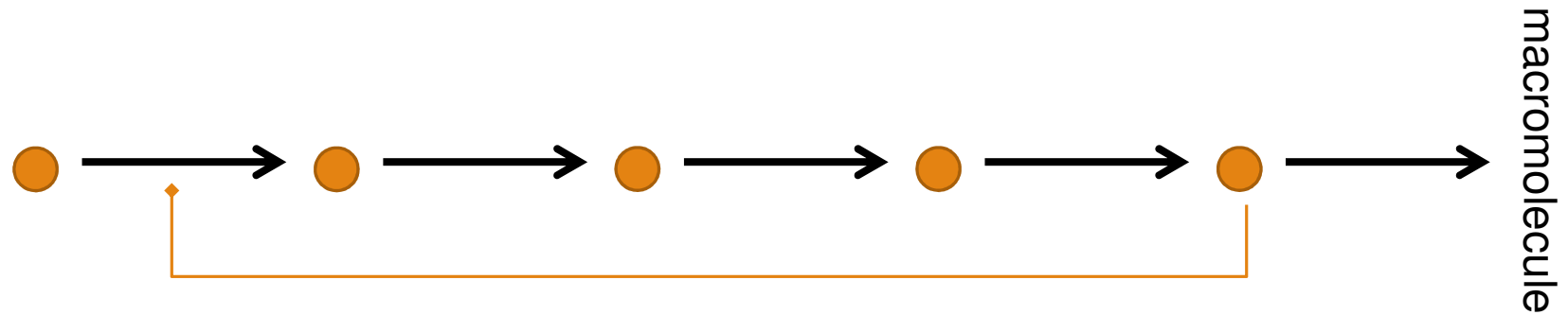
Allosteric inhibitors



Allosteric inhibitors



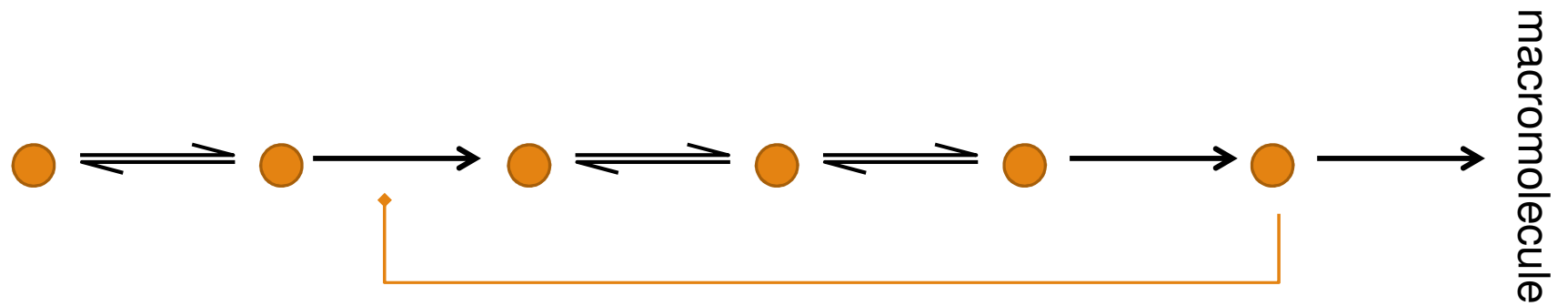
Allosteric regulation



Feed-back inhibition by the last low-molecular weight molecule



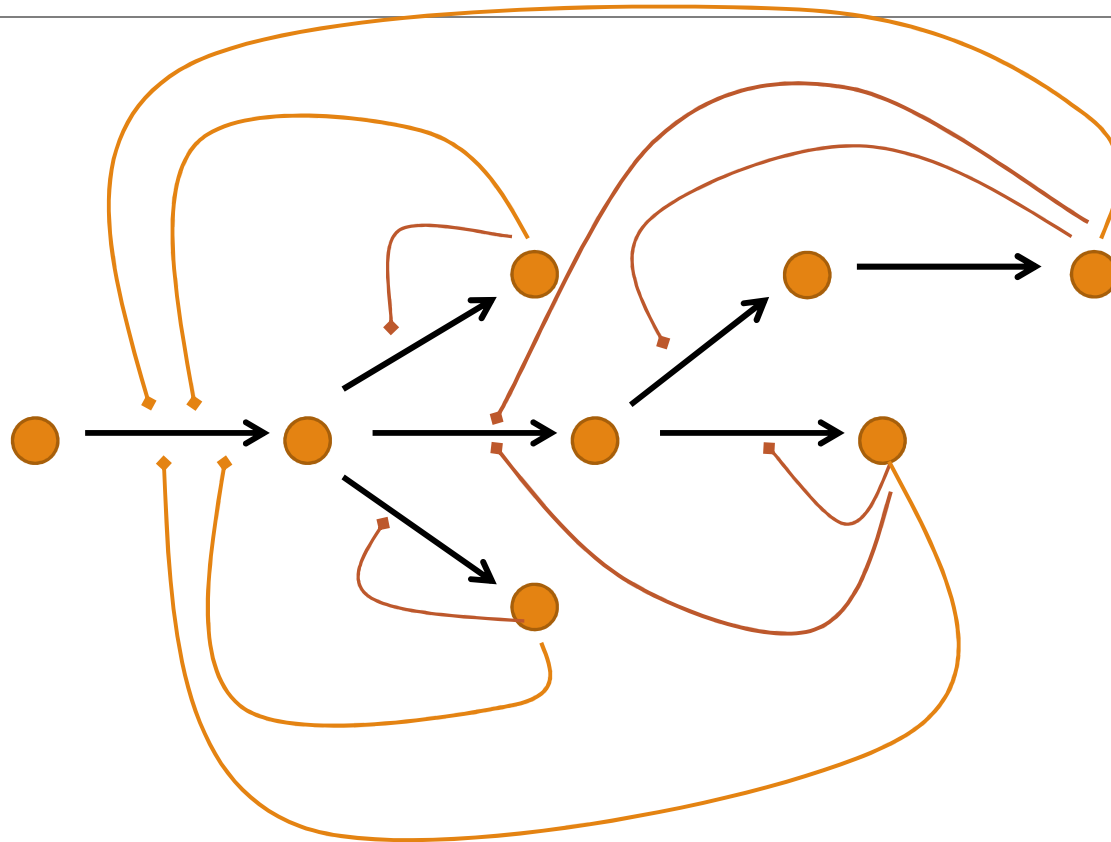
Allosteric regulation



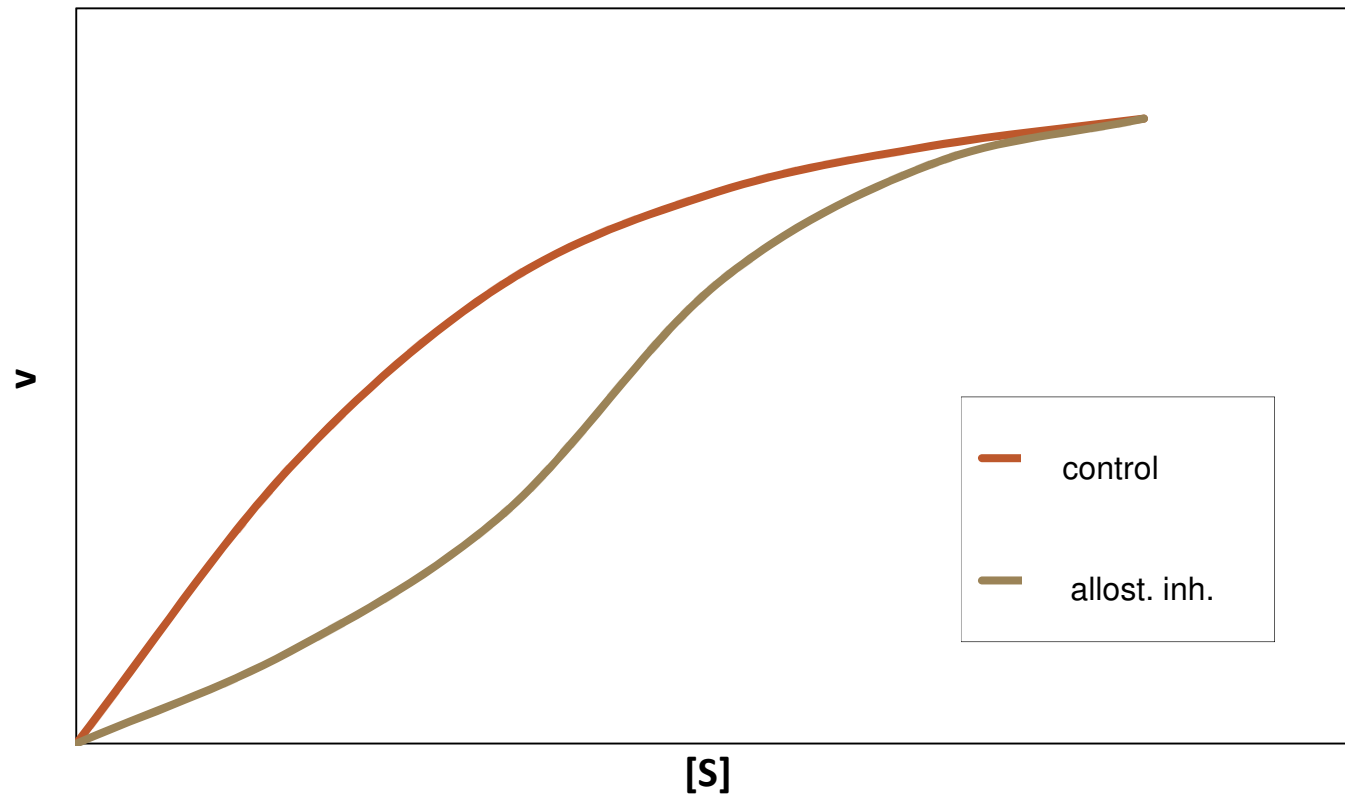
The first irreversible reaction is inhibited



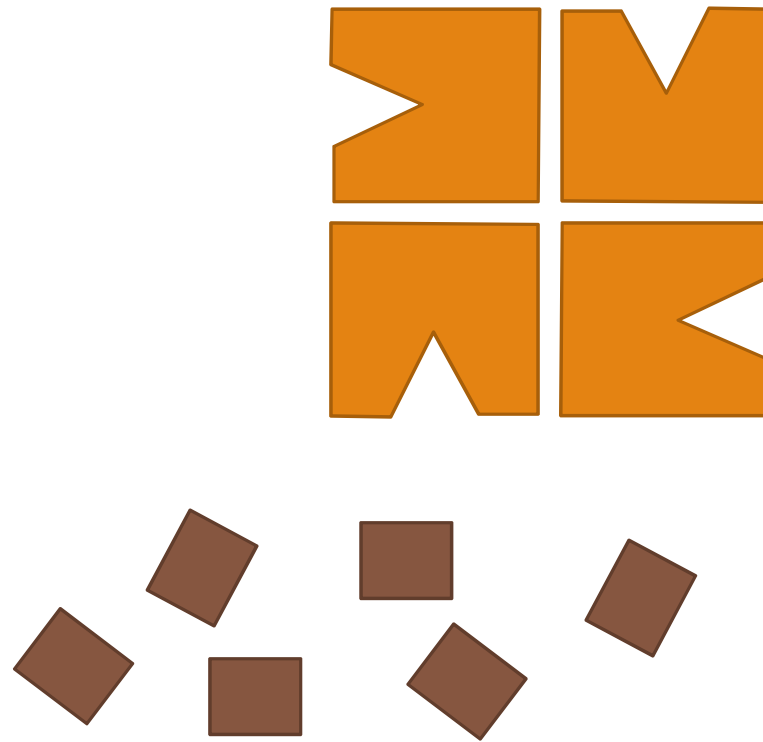
Allosteric regulation



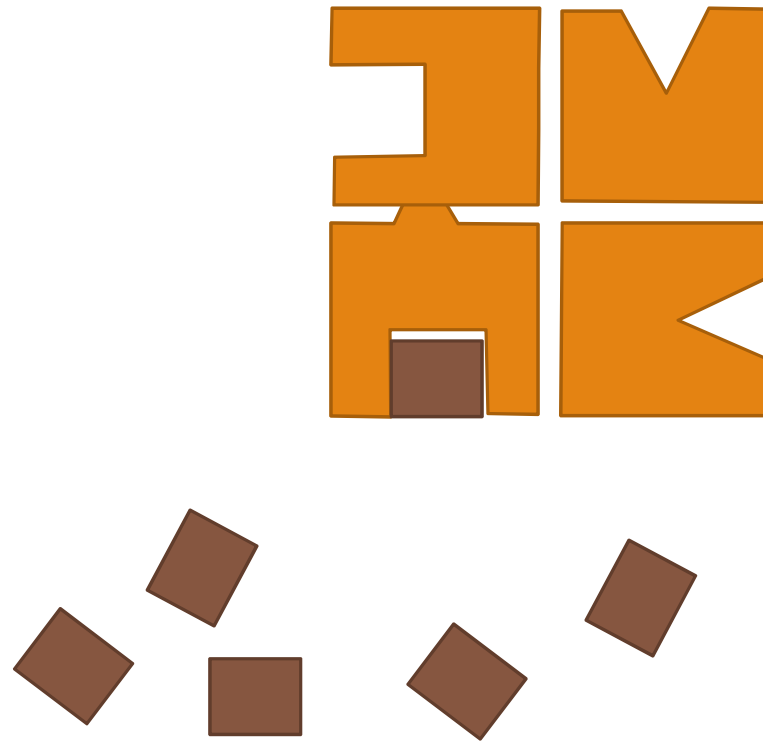
Cooperativity



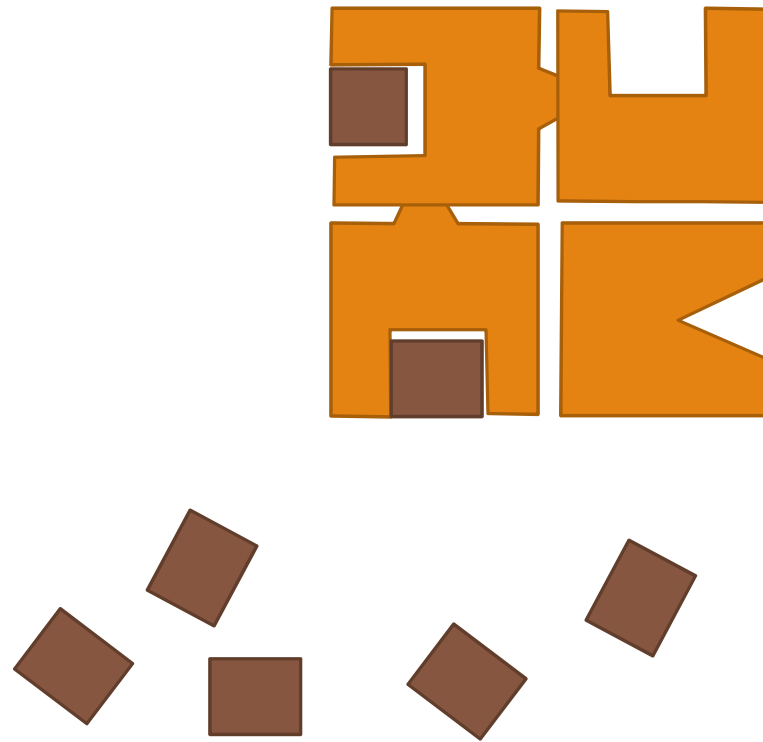
Cooperativity of substrates



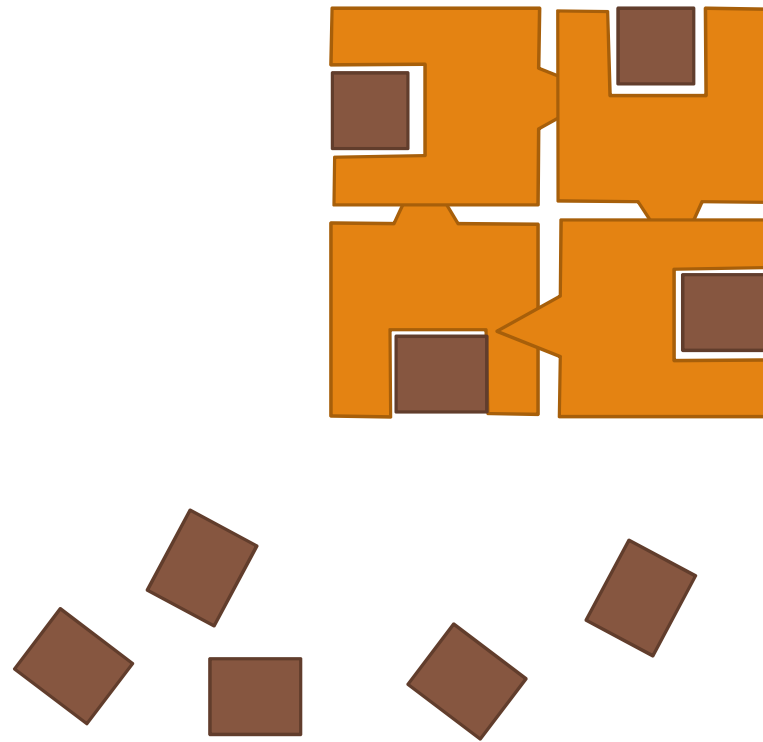
Cooperativity of substrates



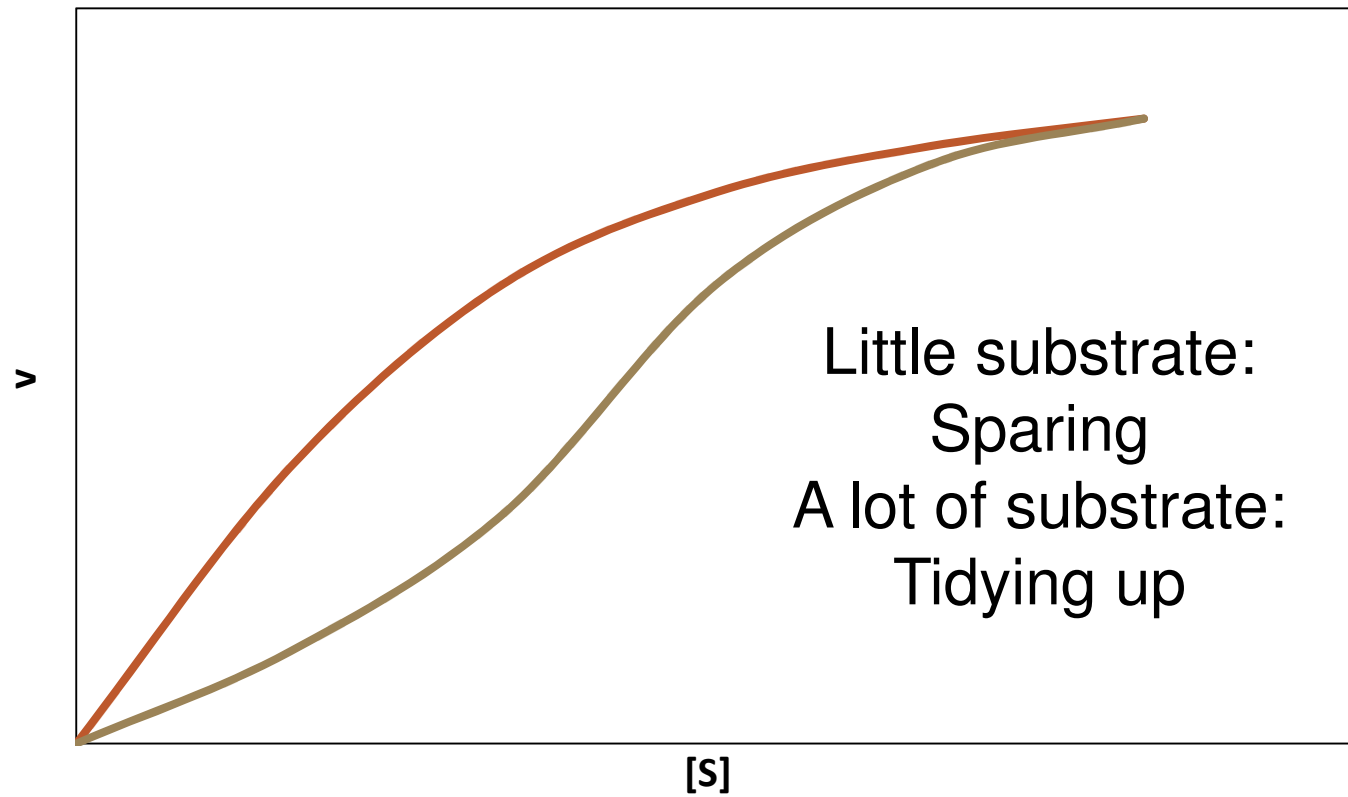
Cooperativity of substrates



Cooperativity of substrates



Cooperativity



Covalent modification

Reversible phosphorylation of –OH

- Beyond active site

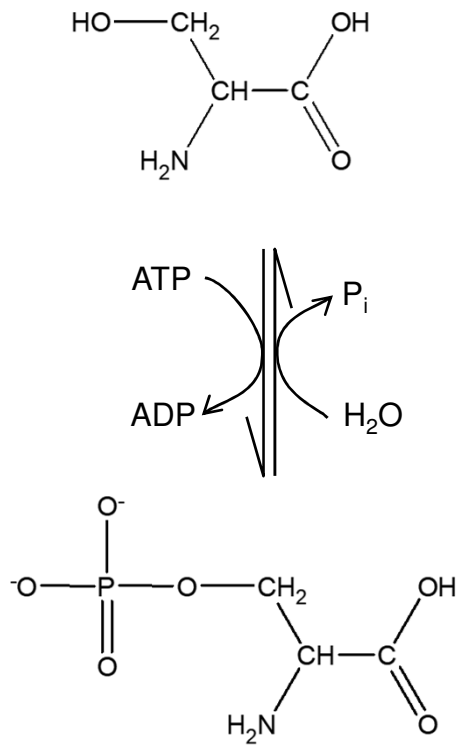
Kinases (phosphate from ATP)

- Ser, Thr
- Tyr

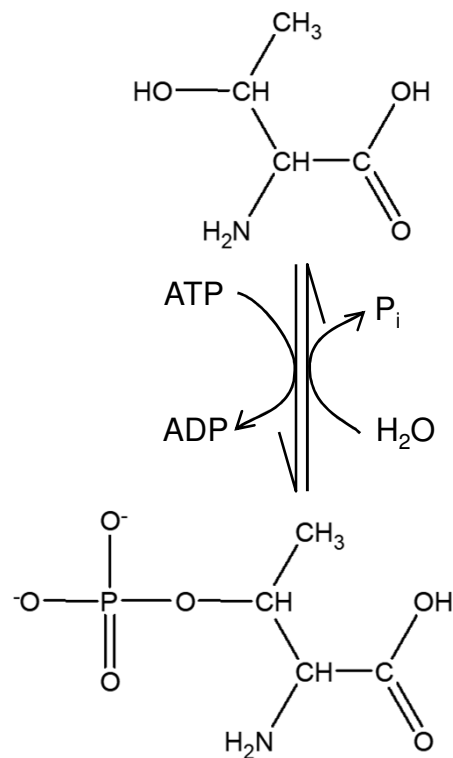
Phosphatases (dephosphorylation – hydrolysis of ester bond)

Phosphorylation

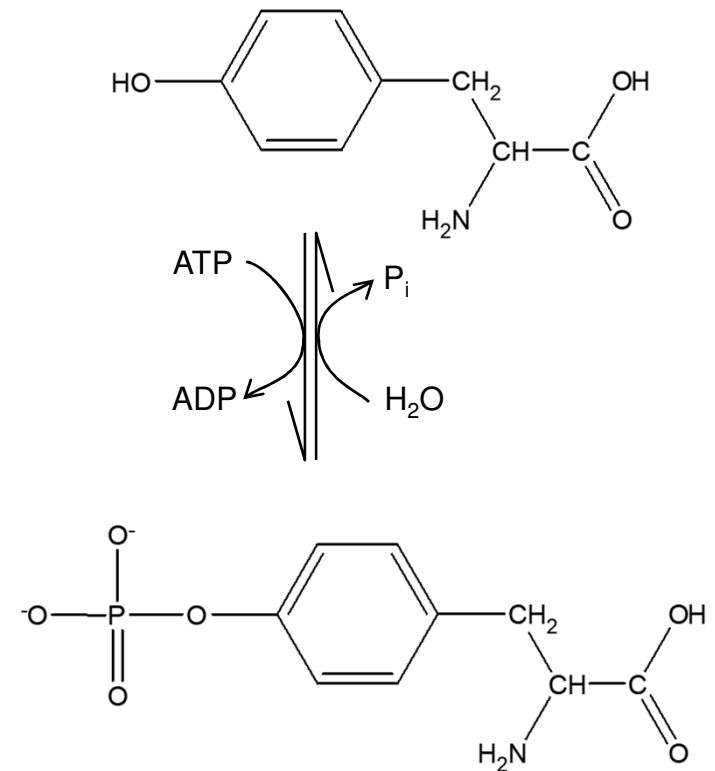
Ser



Thr

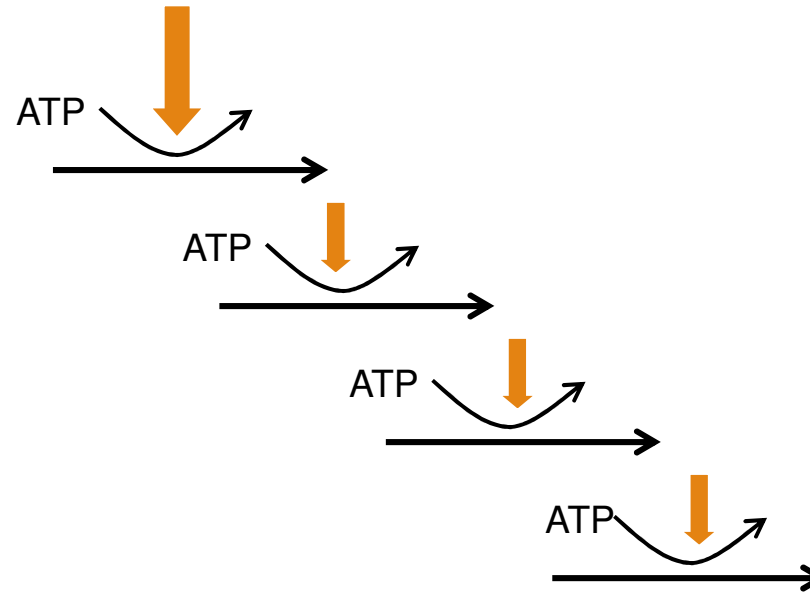


Tyr



Phosphorylation

Neuronal and hormonal regulation



Assembly of subunits

(protein-protein interactions)

Catalytic subunit

Regulatory subunit

- binding cAMP
- calmodulin – binds Ca^{2+}
- G-proteins – bind GTP/GDP
- ...